TRICYCLIC INDOLE HYDROXYETHYLAMINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF ALZHEIMER'S DISEASE.

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of Aβ in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) Physiological Reviews **81**: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. β-amyloid (Aβ) exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) Neuron **27**: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) J. Am. Med. Assoc. **12**: 1571-1577; Younkin, S. (2001) Nat. Med. **1**: 8-19). Aβ is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β-secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of Aβ peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β-secretase) and γ-secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates Aβ. The non-amyloidogenic, α-secretase pathway, which precludes Aβ formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α- and β-secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished Aβ production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) Nat Neurosci. **4**: 231-232; Cai, H. *et. al.* (2001) Nat Neurosci. **4**: 233-234; Roberds, S. L. *et al.* (2001) Hum. Mol. Genet. **10**: 1317-1324).

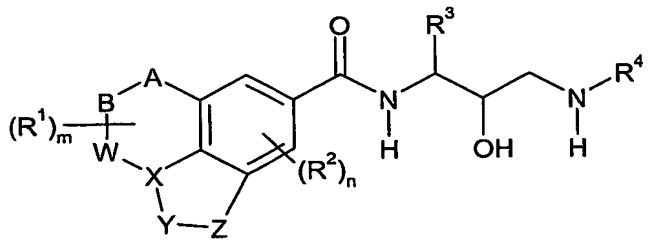
For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally

also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g. Cathepsin D (Connor, G. E. (1998) Cathepsin D in Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woesner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505, WO 02/02506 and WO 03/040096 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β-secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of disease characterised by elevated β-amyloid levels or β-amyloid deposits, such as Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



(I)

wherein

R^1 represents C_{1-3} alkyl or halogen;

R^2 represents C_{1-3} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-3} alkoxy, amino, cyano or n hydroxy;

m represents an integer from 0 to 4;

n represents an integer from 0 to 2;

A-B represents $-NR^5-SO_2-$ or $-NR^5-CO-$;

R^5 represents hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, $-C_{0-6}$ alkyl-aryl, $-C_{0-6}$ alkyl-heteroaryl, $-C_{0-6}$ alkyl-heterocyclyl, $-C_{3-10}$ cycloalkyl-aryl or $-C_{3-10}$ cycloalkyl-heteroaryl;

-W- represents $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(H)=C(H)-$ or $-CH_2-C(H)=C(H)-$;

X-Y-Z represents $-C=CR^8-NR^9-$;

R^8 represents hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl;

R^9 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl, $-C_{0-6}$ alkyl-aryl, $-C_{0-6}$ alkyl-heteroaryl, $-C_{0-6}$ alkyl-heterocyclyl, $-C_{3-10}$ cycloalkyl-aryl, $-C_{3-10}$ cycloalkyl-heteroaryl, $-COOR^{12a}$, $-OR^{12a}$, $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl, $-COC_{3-10}$ cycloalkyl, -CO-aryl, -CO-heteroaryl, $-COC_{1-6}$ alkyl-aryl, $-COC_{1-6}$ alkyl-heteroaryl, $-COC_{3-10}$ cycloalkyl-aryl, $-COC_{3-10}$ cycloalkyl-heteroaryl, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{3-10}$ cycloalkyl , $-SO_2$aryl, –

SO_2heteroaryl, $-SO_2C_{1-6}$ alkyl-aryl, $-SO_2C_{1-6}$ alkyl-heteroaryl, $-SO_2C_{3-10}$ cycloalkyl-aryl or $-SO_2C_{3-10}$ cycloalkyl-heteroaryl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);
R^3 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{0-6} alkyl-aryl, -C_{0-6} alkyl-heteroaryl or $-C_{0-6}$ alkyl-heterocyclyl;
R^4 represents hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} alkynyl, -C_{3-10} cycloalkyl, -C_{3-10} cycloalkenyl, -C_{0-6} alkyl-aryl, -C_{0-6} alkyl-heteroaryl, -C_{0-6} alkyl-heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-aryl, -C_{3-10} cycloalkyl-heteroaryl, -C_{3-10} cycloalkyl-heterocyclyl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^aR^b)$-CONH-C_{3-10} cycloalkyl, -C_{2-6} alkyl-S-C_{1-6} alkyl, -C_{2-6} alkyl-NR^cR^d, -$C(R^aR^b)$-C_{1-6} alkyl, -$C(R^aR^b)$-C_{0-6} alkyl-aryl, -$C(R^aR^b)$-C_{0-6} alkyl-heteroaryl, -$C(R^aR^b)$-C_{0-6} alkyl-heterocyclyl, -C_{2-6} alkyl-O-C_{0-6} alkyl-aryl, -C_{2-6} alkyl-O-C_{0-6} alkyl-heteroaryl or $-C_{2-6}$ alkyl-O-C_{0-6} alkyl-heterocyclyl;
R^a and R^b independently represent hydrogen, C_{1-6} alkyl or R^a and R^b together with the carbon atom to which they are attached may form a C_{3-10} cycloalkyl or heterocyclyl group;
R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a nitrogen containing heterocyclyl group;
wherein said alkyl, alkenyl, alkynyl and cycloalkyl groups may be optionally substituted by one or more (e.g. 1 to 6) halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{2-6} alkenyl, haloC_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkoxy, amino, cyano, hydroxy, $-COOR^{22}$, -S-C_{1-6} alkyl or -C_{1-6} alkyl-NR^6R^7 (wherein R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl) groups; and
wherein said aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (e.g. 1 to 6) C_{1-6} alkyl, halogen, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, oxo, hydroxy, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, $-COOR^{22}$, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$, $-SO_2NR^{22}R^{23}$, $-NR^{22}R^{23}$, -C_{1-6} alkyl-$NR^{22}R^{23}$, -C_{1-6} alkyl-O-C_{1-6} alkyl or -C_{1-6} alkanoyl groups (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl);
or a pharmaceutically acceptable salt or solvate thereof.

Specific compounds which may be mentioned are those wherein
R^5 represents hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{3-10} cycloalkyl-aryl or -C_{3-10} cycloalkyl-heteroaryl; and
R^9 represents hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{3-10} cycloalkyl-aryl, -C_{3-10} cycloalkyl-heteroaryl, $-COOR^{12a}$, $-OR^{12a}$, $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl, $-COC_{3-10}$ cycloalkyl, -CO-aryl, -CO-heteroaryl, $-COC_{1-6}$ alkyl-aryl, $-COC_{1-6}$ alkyl-heteroaryl, $-COC_{3-10}$ cycloalkyl-aryl, $-COC_{3-10}$ cycloalkyl-heteroaryl, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{3-10}$ cycloalkyl , $-SO_2$aryl, $-SO_2$heteroaryl, $-SO_2C_{1-6}$ alkyl-aryl, $-SO_2C_{1-6}$ alkyl-heteroaryl, $-SO_2C_{3-10}$ cycloalkyl-aryl or $-SO_2C_{3-10}$

cycloalkyl-heteroaryl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl); and

R^3 represents optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl; and

R^4 represents hydrogen, optionally substituted C_{1-10} alkyl, -C_{3-10} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-aryl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^aR^b)$-CONH-C_{3-10} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^cR^d, -$C(R^aR^b)$-C_{1-6} alkyl, -$C(R^aR^b)$-C_{0-6} alkyl-aryl, -$C(R^aR^b)$-C_{0-6} alkyl-heteroaryl, -$C(R^aR^b)$-C_{0-6} alkyl-heterocyclyl, -C_{1-6} alkyl-O-C_{0-6} alkyl-aryl, -C_{1-6} alkyl-O-C_{0-6} alkyl-heteroaryl or -C_{1-6} alkyl-O-C_{0-6} alkyl-heterocyclyl; and

R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a heterocyclyl group; and

optional substituents for alkyl groups of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{12a}, R^{13a}, R^a, R^b, R^c and R^d include one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano, hydroxy or -C_{1-6} alkyl-NR^6R^7 (wherein R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl); and

wherein said aryl, heteroaryl or heterocyclyl groups of R^3, R^4, R^5 and R^9 may be optionally substituted by one or more (e.g. 1, 2 or 3) C_{1-6} alkyl, halogen, -CF_3, -OCF_3, oxo, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, -$NR^{22}COR^{23}$, -$CONR^{22}R^{23}$ -C_{1-6} alkyl-$NR^{22}R^{23}$ (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-10} cycloalkyl), -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkanoyl or hydroxy groups; or a pharmaceutically acceptable salt or solvate thereof.

The term 'C_{x-y} alkyl' as used herein as a group or a part of the group refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like.

The term 'C_{x-y} alkenyl' as used herein refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds and having from x to y carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl or hexenyl and the like.

The term 'C_{x-y} alkynyl' as used herein refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds and having from x to y carbon atoms. Examples of such groups include ethynyl, propynyl, butynyl, pentynyl or hexynyl and the like.

The term 'C_{x-y} alkoxy' as used herein refers to an –O-C_{x-y} alkyl group wherein C_{x-y} alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like.

The term 'C_{x-y} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of x to y carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like.

The term 'C_{x-y} cycloalkenyl' as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of x to y carbon atoms containing one or more carbon-carbon double bonds. Examples of such groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom.

The term 'haloC_{x-y} alkyl' as used herein refers to a C_{x-y} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like.

The term 'haloC_{x-y} alkoxy' as used herein refers to a C_{x-y} alkoxy group as herein defined wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include difluoromethoxy or trifluoromethoxy and the like.

The term 'aryl' as used herein refers to a C_{6-12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl or tetrahydronaphthalenyl and the like.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such fused aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of such monocyclic

rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

The term 'nitrogen containing heterocyclyl' is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

Preferably, A-B represents $-NR^5-SO_2-$.

Preferably, R^5 represents hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl or isopropyl) or $-C_{0-6}$ alkyl-aryl (e.g. phenyl or benzyl), more preferably C_{1-6} alkyl (e.g. methyl, ethyl or isopropyl), most preferably methyl or ethyl, especially methyl.

Preferably, m represents 0 or 1, more preferably 0.

Preferably, n represents 0 or 1, more preferably 0.

Preferably, R^8 represents hydrogen.

Preferably, R^9 represents hydrogen or C_{1-6} alkyl (e.g. ethyl, propyl, isopropyl or butyl), more preferably ethyl.

Preferably, W represents $-(CH_2)_2-$ or $-C(H)=C(H)-$, more preferably $-(CH_2)_2-$.

Preferably, R^3 represents $-C_{0-6}$ alkyl-aryl (e.g. benzyl) optionally substituted by one or two halogen atoms (e.g. fluorine or chlorine). More preferably, R^3 represents unsubstituted benzyl.

Preferably, R^4 represents

$-C_{1-10}$ alkyl (e.g. ethyl, propyl, 1-methylpropyl, butyl, 3-methylbutyl, 2-ethylbutyl, 1-propylbutyl, 3,3-dimethylbutyl, 1,5-dimethylhexyl or 1,1,5-trimethylhexyl) optionally substituted by one or more halogen (e.g. 2-fluoroethyl, 3-fluoropropyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl or 2,2,3,3,3-pentafluoropropyl), C_{1-6} alkoxy (e.g. methoxy or propoxy), haloC_{1-6} alkoxy (e.g. 2,2,2-trifluoroethoxy) or $-S-C_{1-6}$ alkyl (e.g. –S-methyl, –S-ethyl or –S-t-Bu) groups;

$-C_{2-10}$ alkenyl (e.g. propenyl or butenyl) optionally substituted by one or more C_{1-6} alkyl groups (e.g. 2-methyl-2-propen-1-yl or 3-methyl-2-buten-1-yl);

-C_{3-10} alkynyl (e.g. propynyl, butynyl or pentynyl) optionally substituted by one or more C_{1-6} alkyl groups (e.g. 1,1-dimethyl-2-propyn-1-yl);

-C_{3-10} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclohexyl, cycloheptyl, cyclooctyl, tricyclodecyl or bicycloheptyl) optionally substituted by one or more halogen (e.g. fluorine), C_{1-6} alkyl (e.g. methyl, ethyl or propyl) or -C_{2-6} alkynyl (e.g. ethynyl) groups;

-C_{3-10} cycloalkenyl (e.g. cyclopentenyl);

-C_{1-6} alkyl-C_{3-10} cycloalkyl (e.g. –CH_2-cyclopropyl or –$(CH_2)_2$-cyclohexyl);

-C_{0-6} alkyl-aryl (e.g. benzyl or phenyl) optionally substituted by one or more halogen (e.g. chlorine), cyano, haloC_{1-6} alkoxy (e.g. -OCF_3), haloC_{1-6} alkyl (e.g. -CF_3), C_{1-6} alkyl (e.g. methyl), C_{1-6} alkoxy (e.g. methoxy) or -$NR^{22}R^{23}$ (e.g. –$N(Me)_2$) groups;

-C_{0-6} alkyl-heteroaryl (e.g. –CH_2-pyrazolyl, - CH_2-pyridinyl, - CH_2-thienyl or – CH_2-isoxazolyl) optionally substituted by one or more halogen, cyano, haloC_{1-6} alkoxy (e.g. -OCF_3), haloC_{1-6} alkyl (e.g. -CF_3 or trifluoroethyl), C_{1-6} alkyl (e.g. methyl or ethyl) or C_{1-6} alkoxy (e.g. methoxy) groups;

-$C(R^aR^b)$-CONH-C_{3-10} cycloalkyl (e.g. -$C(R^aR^b)$-CONH-cyclohexyl);

-C_{3-10} cycloalkyl-aryl; or

-C_{0-6} alkyl-heterocyclyl (e.g. tetrahydropyranyl) optionally substituted by one or more C_{1-6} alkyl (e.g. methyl) groups.

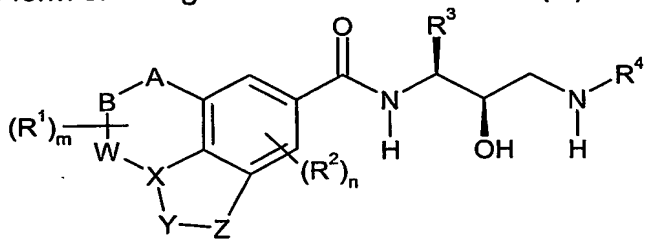
Preferably, R^a and R^b independently represent hydrogen, methyl or together with the carbon atom to which they are attached form a cyclopropyl or cyclohexyl group, more preferably R^a and R^b both represent hydrogen.

Preferred compounds according to the invention includes examples E1-E90 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic or organic acids e.g. hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):

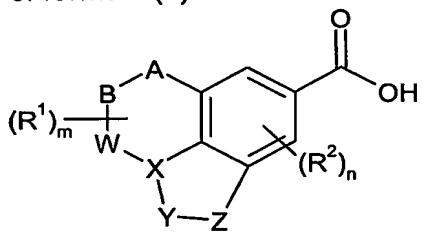


(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

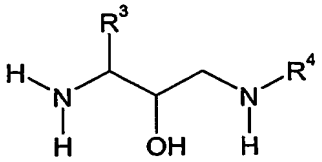
A process according to the invention for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (II)



(II)

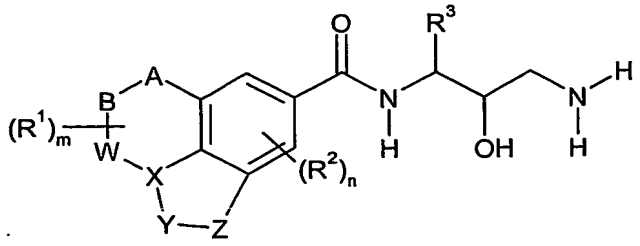
or an activated and/or optionally protected derivative thereof wherein R^1, R^2, m, n, A, B, W, X, Y and Z are as defined above, with a compound of formula (III)



(III)

wherein R^3 and R^4 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive alkylation of a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3, m, n, A, B, W, X, Y and Z are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Where the compound of formula (II) is an activated derivative, (e.g. by activation of a carboxylic acid to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), process (a) typically comprises treatment of said activated derivative with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid of formula (II) and amine are preferably reacted in the presence of an activating agents such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT), or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)

Where the compound of formula (II) is a carboxylic acid, process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, e.g. between 0°C and room temperature.

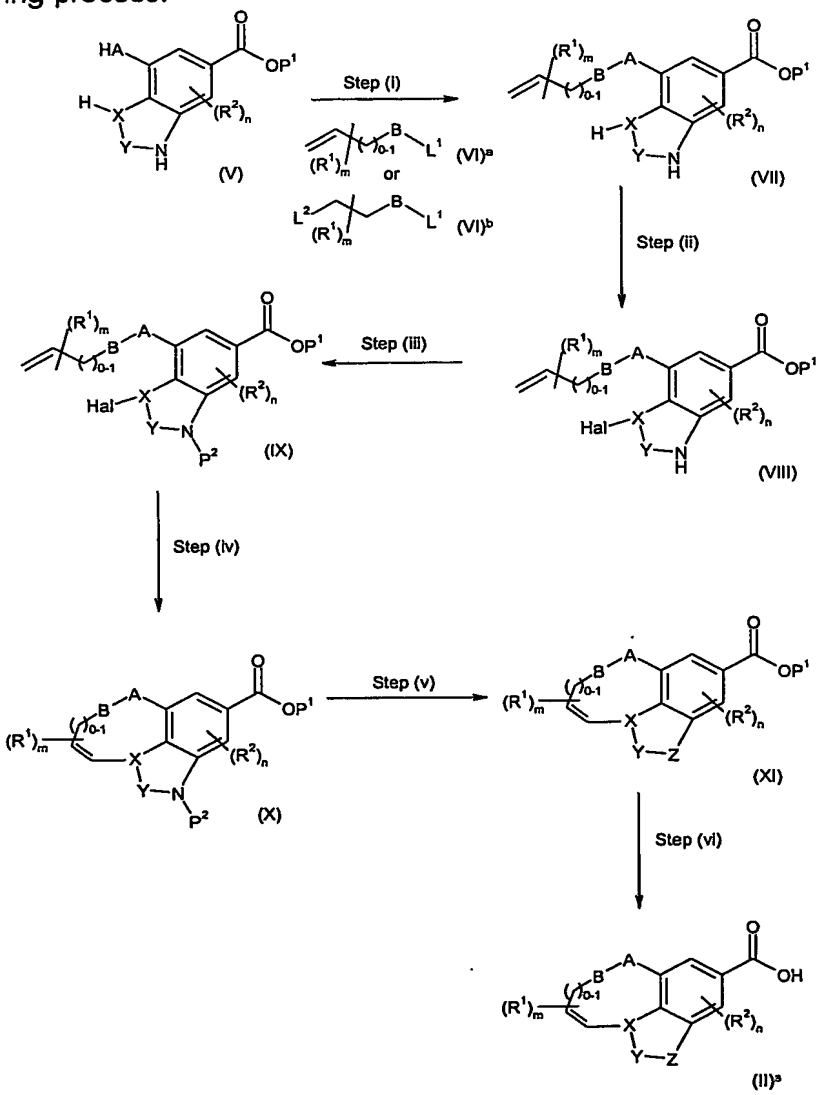
Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol, dichloromethane and 1,2-dichloroethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$)

which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyldimethylsilyl, which may be removed using standard methods, for example use of an acid such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation. For example, compounds of formula (I) wherein W represents –C(H)=C(H)- or –CH_2-C(H)=C(H)- may be converted to compounds of formula (I) wherein W represents -$(CH_2)_2$- or -$(CH_2)_3$- by catalytic hydrogenation compounds as herein described.

Compounds of formula (II) and/or activated and optionally protected derivatives thereof wherein W represents –C(H)=C(H)- or –CH_2-C(H)=C(H)- may be prepared in accordance with the following process:



wherein R^1, R^2, m, n, A, B, X, Y and Z are as defined above, P^1 represents a suitable group such as C_{1-6} alkyl, P^2 represents a suitable group such as $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl or $-SO_2$aryl, L^1 and L^2 independently represent a suitable leaving group such as a halogen atom (e.g. chlorine) and Hal represents a halogen atom, such as bromine or iodine.

Step (i) typically comprises reaction of a compound of formula (V) with a compound of formula $(VI)^a$ or $(VI)^b$ in the presence of a suitable base such as pyridine in the presence of a suitable reagent, e.g. DMAP and a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature.

Step (ii) typically comprises the use of a halogen such as bromine in the presence of a suitable solvent such as dimethylformamide at a suitable temperature, such as room temperature.

Step (iii) typically comprises introduction of an N-protecting group using standard protocols. For example, an acetate group can be introduced by treatment with acetic anhydride in the presence of a suitable solvent such as pyridine at a suitable temperature, such as room temperature.

Step (iv) typically comprises a standard procedure for addition of a vinyl halide to an alkene, such as the use of a mixture of tetrabutylammonium chloride, palladium acetate and triorthotolyl phosphine in an appropriate solvent such as tetrahydrofuran at an appropriate temperature such as 65°C.

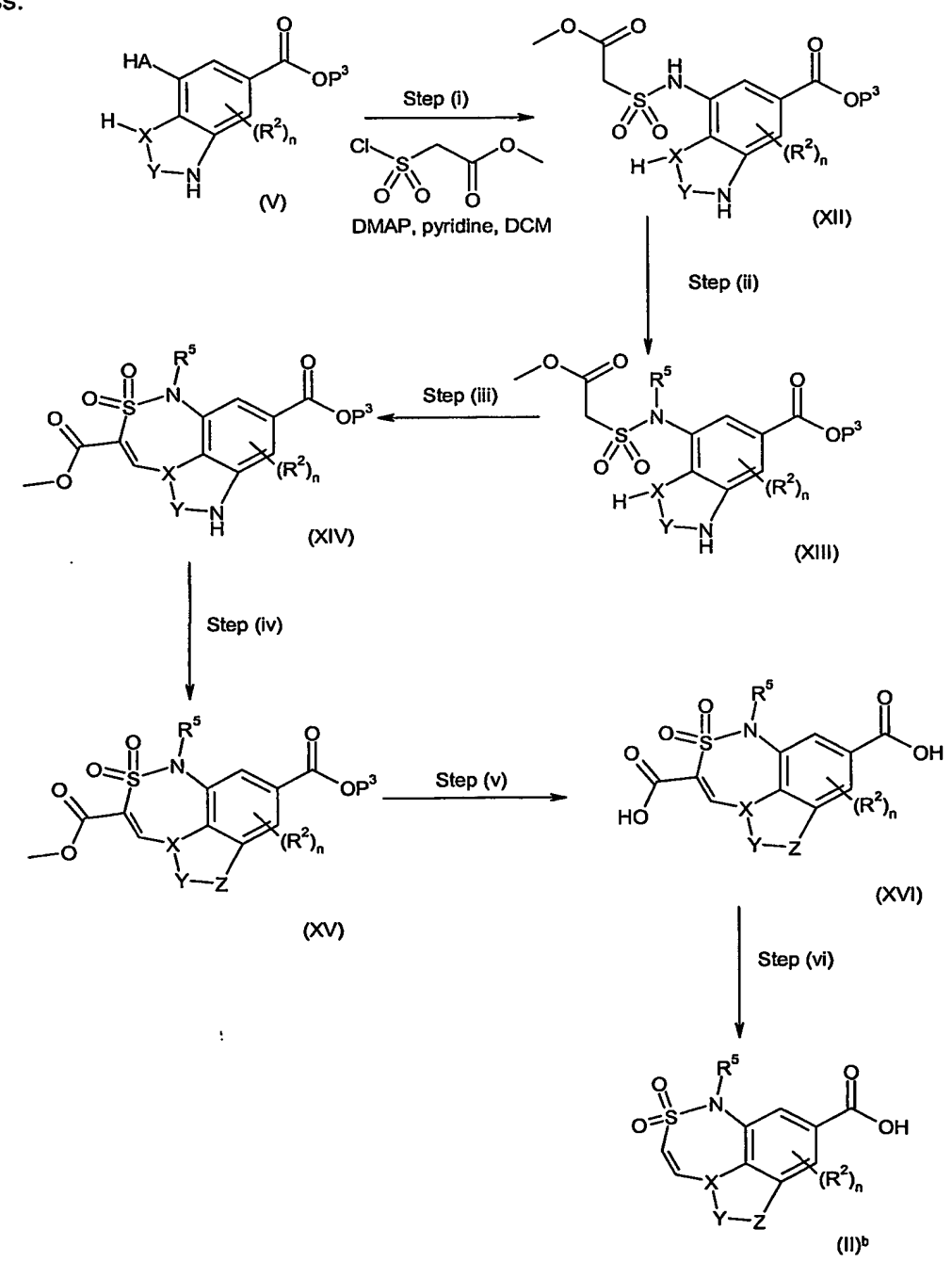
Step (v) typically comprises the use of standard deprotection conditions (e.g. treatment with a suitable amine such as triethylamine in a suitable solvent such as ethanol at an appropriate temperature such as 80°C) and subsequent derivatisation of Z using standard methods (e.g. treatment with a base such as sodium hydride and an alkylating agent such as ethyl iodide in a suitable solvent such as dimethylformamide at an appropriate temperature such as room temperature).

Step (vi) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt such as lithium or sodium salt in an appropriate solvent such as methanol at an appropriate temperature such as 50°C. In the case of a tert-butyl ester this conversion can be achieved by the use of an appropriate acid such as trifluoroacetic acid in an appropriate solvent such as dichloromethane at an appropriate temperature such as 0 °C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (II) wherein W represents $-(CH_2)_2-$ or $-(CH_2)_3-$ may be prepared in an identical manner to the process described above except an additional step is required

in which compounds of formula (XI) are hydrogenated prior to step (vi). This step, typically comprises the use of standard reducing conditions such as treatment with 10% palladium on charcoal and ammonium formate in a suitable solvent such as methanol at a suitable temperature e.g. reflux.

Compounds of formula (II) wherein W represents –C(H)=C(H)-, A-B represents -NR^5-SO_2- and m represents 0 may also be prepared in accordance with the following process:



wherein R^2, n, R^5, X, Y and Z are as defined above and P^3 represents a suitable group such as C_{1-6} alkyl.

Step (i) typically comprises reaction of a compound of formula (V) with methyl (chlorosulfonyl)acetate in the presence of a suitable base such as pyridine in the presence of a suitable reagent, e.g. DMAP and a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature.

Step (ii) typically comprises reaction with an alkyl halide such as iodomethane in the presence of a suitable base such as potassium carbonate and a suitable solvent such as dimethylformamide at a suitable temperature such as room temperature.

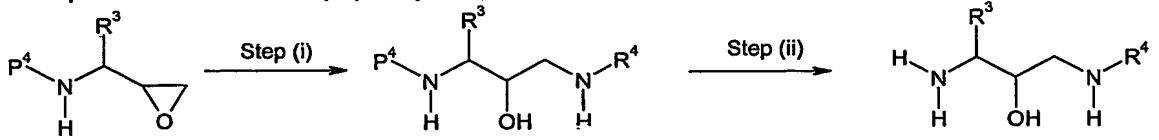
Step (iii) typically comprises reaction with a reagent prepared by mixing together phosphorus oxychloride and dimethylformamide in the presence of a suitable solvent such as dimethylformamide at a suitable temperature, such as 60°C.

Step (iv) typically comprises reaction with an alkyl halide such as iodoethane in the presence of a suitable base such as sodium hydride and a suitable solvent such as dimethylformamide at a suitable temperature such as room temperature.

Step (v) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt like lithium or sodium salt in an appropriate solvent such as methanol at an appropriate temperature such as 65°C

Step (vi) typically comprises a standard procedure for decarboxylation such as treatment with an acid such as hydrogen chloride in a suitable solvent such as dioxane at a suitable temperature such as 100°C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (III) may be prepared in accordance with the following process:



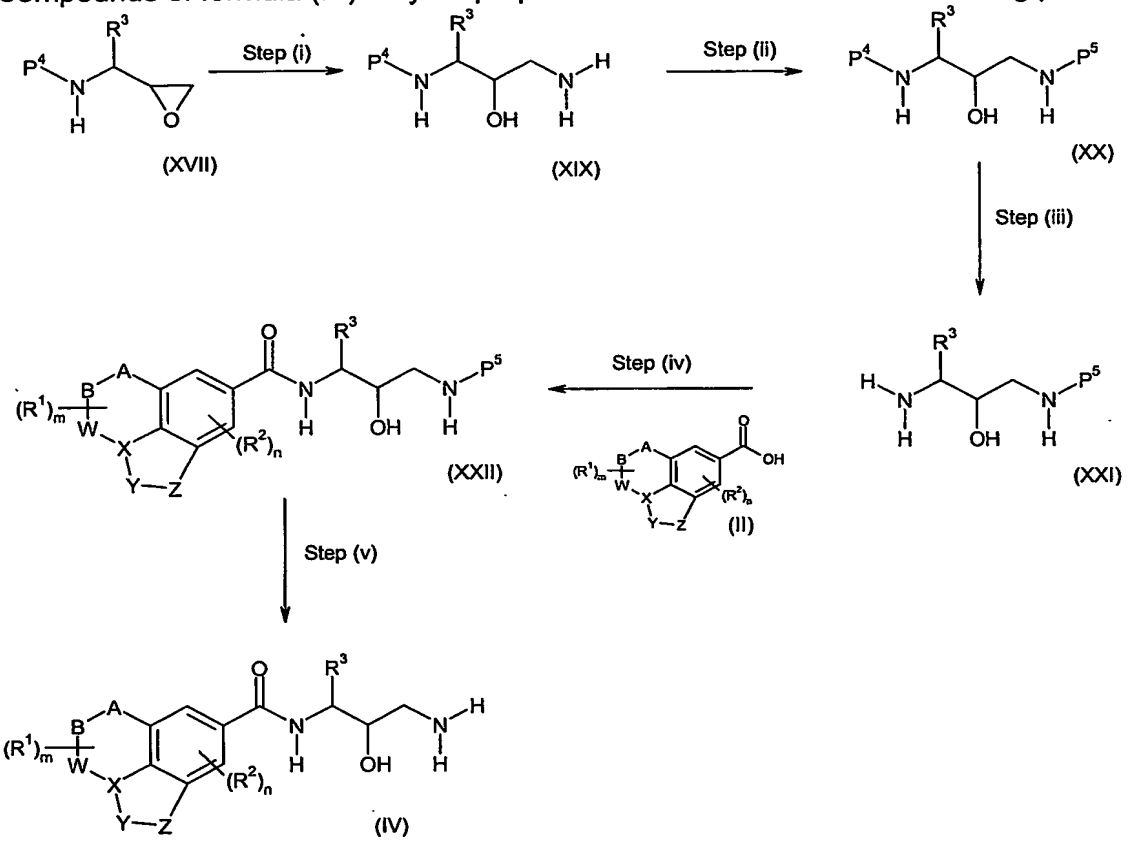
(XVII) (XVIII) (III)

wherein R^3 and R^4 are as defined above and P^4 represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (XVII) with a compound of formula NH_2R^4 in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), e.g. when P^4 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1, R^2, R^3, m, n, A, B, W, X, Y, Z and P^4 are as defined above and P^5 represents a suitable amine protecting group different to P^4, such as -$COOCH_2$-phenyl.

Step (i) typically comprises the reaction of a compound of formula (XVII) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

When P^5 represents -$COOCH_2$-phenyl, step (ii) typically comprises the use of $ClCOOCH_2$-phenyl in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), e.g. when P^4 represents t-butoxycarbonyl, deprotection typically

comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Step (iv) typically comprises reacting a compound of formula (XXI) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (v) typically comprises the use of suitable deprotection reactions as described above for process (c), e.g. when P^5 represents -$COOCH_2$-phenyl, deprotection typically comprises the use of a suitable catalyst, e.g. palladium in the presence of a suitable solvent, e.g. water and ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, e.g. 60°C.

Compounds of formula (V), $(VI)^a$, $(VI)^b$ and (XVII) are either commercially available or may be prepared from commercially available compounds using standard procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β-amyloid levels or β-amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope

pharmaceutical compositions for use in the therapy of diseases characterised by elevated β-amyloid levels or β-amyloid deposits, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β-amyloid levels or β-amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β-amyloidosis of the Dutch type, cerebral β-amyloid angiopathy and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β-amyloid levels or β-amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents. Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), gamma secretase inhibitors, anti-inflammatory agents (such as cyclooxygenase II inhibitors), antioxidants (such as Vitamin E and ginkolidesor), statins or p-glycoprotein (P-gp) inhibitors (such as cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 and 918).

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before

use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were

specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Preparation of Intermediates

Description 1

Methyl 4-methyl-3,5-dinitrobenzoate (D1)

Thionyl chloride (72 g, 615 mmol) was added dropwise, with stirring, to a suspension of 4-methyl-3,5-dinitrobenzoic acid (commercially available from Aldrich)(100 g, 440 mmol) in methanol (300 ml). The resulting solution was left to stand at room temperature overnight and the precipitate that formed was then collected by filtration. The filtrate was washed with cold methanol to give the title compound (D1) as a white solid (104 g, 430 mmol) which was used in the next step without further purification.

Description 2

Methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D2)

A solution of methyl 4-methyl-3,5-dinitrobenzoate (D1) (40 g, 170 mmol) in dimethylformamide (50 ml) was treated with N,N-dimethylformamide dimethyl acetal (50 ml, 380 mmol) and the resulting mixture was heated at 50°C for 1 h. The solvent was then evaporated and the residue was triturated with diethyl ether/i-hexane (1:1) to give crude title compound (D2) (40 g, 136 mmol) as a dark red solid. This was used in subsequent reactions without further purification.

Description 3

Methyl 4-amino-1*H*-indole-6-carboxylate (D3)

Methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D2) (10.0 g, 34 mmol) in methanol (150 ml) was treated with ammonium formate (21.4 g, 340 mmol) and wet (50% water) 10% palladium on carbon (3 g) under a nitrogen atmosphere. The mixture was then heated at 50°C for 1 h. The mixture was filtered and the solvent was removed by evaporation. The residue was dissolved in ethyl acetate (200 ml) and washed with saturated aqueous sodium hydrogen carbonate (100 ml). The organic phase was then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether/i-hexane (1:1) to give the title compound (D3) (5.0 g, 26 mmol) as a pale pink solid which was used in subsequent reactions without further purification. $[M+H]^+$ = 191.1, RT = 2.17 min.

Description 4

Methyl 4-[(ethenylsulfonyl)amino]-1*H*-indole-6-carboxylate (D4)

To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (D3)(2.0 g, 10.5 mmol) in dichloromethane (100 ml) was added triethylamine (2.13 g, 21 mmol) and the mixture was heated gently to dissolve any remaining solids. 2-Chloro-1-ethane sulfonyl chloride (1.63 g, 10 mmol) was then added dropwise to the mixture and stirring continued for 30

min. At this point a further quantity of 2-chloro-1-ethane sulfonyl chloride (0.39 g, 2.4 mmol) was added and stirring continued for a further 30 min. The mixture was washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml) and then the organic phase was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was triturated with diethyl ether/i-hexane (1:1) to give crude title compound (D4)(1.6 g, 5.7 mmol) as a brown solid which was used in subsequent reactions without further purification. $[M+H]^+$ = 281.1, RT = 2.23 min.

Description 5

Methyl 4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D5)

A solution of methyl 4-[(ethenylsulfonyl)amino]-1*H*-indole-6-carboxylate (D4)(5.0 g, 17.9 mmol) in dimethylformamide (50 ml) was treated with potassium carbonate (2.48 g, 18 mmol) and iodomethane (1.12 ml, 18 mmol) at room temperature for 90 min. Diethyl ether (200 ml) was added to the mixture and the mixture was then washed sequentially with 2M aqueous hydrogen chloride (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml) and water (3 x 100 ml). The aqueous phase was then dried over magnesium sulfate and then filtered and evaporated *in vacuo* to give the title compound (D5)(4.5 g, 15.3 mmol) as a brown foam. This was used without further purification in subsequent reactions. $[M+H]^+$ = 295.1, RT = 2.48 min.

Description 6

Methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D6)

Methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D6) was obtained in an analogous manner to that described for the synthesis of (D5) but using iodoethane in the place of iodomethane. $[M+H]^+$ = 309.1, RT = 2.65 min.

Description 7

Methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D7)

A solution of methyl 4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D5)(0.700 g, 2.4 mmol) in dimethylformamide (20 ml) was treated dropwise with a solution of bromine (0.12 ml, 2.3 mmol) in dimethylformamide (5 ml) over 15 min. The solvent was then evaporated *in vacuo* and the residue taken up in ethyl acetate (50 ml) and washed with water (2 x 50 ml). The organic phase was then dried over magnesium sulfate, filtered and evaporated to give the title compound (D7)(0.800 g, 2.2 mmol) as a pale brown foam. $[M+H]^+$ = 373.0, RT = 2.74 min.

Description 8

Methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D8)

Methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D8) was obtained in an analogous manner to that described for the synthesis of (D7) but using methyl 4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D6) in the place of

methyl 4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D5). $[M+H]^+$ = 389.1, RT = 2.89 min.

Description 9

Methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D9)

A solution of methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D7)(0.800 g, 2.2 mmol) in pyridine (5 ml) was treated with acetic anhydride (1 ml, 10.6 mmol) and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate (50 ml) and washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate and then filtered and evaporated *in vacuo*. The crude product was recrystallised from ethyl acetate/*i*-hexane to obtain the title compound (D9)(0.510 g, 1.23 mmol) as a pink solid. $[M+H]^+$ = 417.0, RT = 2.85 min.

Description 10

Methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10)

Methyl-1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10) was obtained in an analogous manner to that described for the synthesis of (D9) but using methyl 3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D8) in the place of methyl 3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D7). RT = 3.01 min

Description 11

Methyl 1-ethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D11)

A solution of methyl-1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10)(0.400 g, 0.94 mmol) in tetrahydrofuran (30 ml) was treated with tetrabutylammonium chloride (0.560 g, 2.0 mmol), palladium diacetate (0.220 g, 1.0 mmol), and triorthotolyl phosphine (0.304 g, 2.0 mmol) under a nitrogen atmosphere. The mixture was heated at reflux for 30 min. The solvent was evaporated and the residue was dissolved in ethyl acetate (100 ml) and washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate and then filtered and evaporated *in vacuo*. The residue was now dissolved in ethanol (50 ml) and treated with triethylamine (0.5 ml, 3.5 mmol). The mixture was then heated at reflux for 15 min before cooling and workup as described above gave the crude product which was crystallised from ethyl acetate/*i*-hexane to give the title compound (D11)(0.280 g, 0.92 mmol) as a brown solid which was used in subsequent reactions without further purification. $[M+H]^+$ = 307.1, RT = 2.54 min

Description 12

Methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12)

Methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12) was obtained in an analogous manner to that described for the synthesis of (D11) but using methyl 1-acetyl-3-bromo-4-[(ethenylsulfonyl)(methyl)amino]-1*H*-indole-6-carboxylate (D9) in the place of methyl-1-acetyl-3-bromo-4-[(ethenylsulfonyl)(ethyl)amino]-1*H*-indole-6-carboxylate (D10). $[M+H]^+$ = 293.1 ,RT = 2.37 min

Description 13

Methyl 1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D13)

A solution of methyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D12)(0.400 g, 1.37 mmol) in methanol (50 ml) was treated with ammonium formate (0.800 g, 12.7 mmol) and 10% palladium on charcoal (0.4 g) and the mixture was heated at reflux for 3.5 h. The mixture was then filtered and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml) then dried over magnesium sulfate. Filtration and evaporation *in vacuo* gave the title compound (D13)(0.220 g, 0.75 mmol) as a brown solid. This was used in subsequent reactions without further purification. $[M+H]^+$ = 295.1, RT = 2.32 min

Description 14

Methyl 4-({[2-(methyloxy)-2-oxoethyl]sulfonyl}amino)-1*H*-indole-6-carboxylate (D14)

A solution of methyl 4-amino-1*H*-indole-6-carboxylate (D3) (9 g, 47 mmol) in dichloromethane (180 ml) was treated with pyridine (5.8 ml) and DMAP (0.577 g) and then methyl (chlorosulfonyl)acetate [56146-83-9] (8.63 g, 50 mmol) was added dropwise. The resulting black mixture was stirred at room temperature overnight. An additional quantity of methyl (chlorosulfonyl)acetate (1.2 g) was added and the mixture stirred for a further 48 hours at room temperature. The mixture was diluted with ethyl acetate and washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting solid was triturated with ether to give the crude title compound (D14) as a brown solid (9.37 g). $[M-H]^-$ = 325.2, RT = 2.14 min

Description 15

Methyl 4-(methyl{[2-(methyloxy)-2-oxoethyl]sulfonyl}amino)-1*H*-indole-6-carboxylate (D15)

A solution of methyl 4-({[2-(methyloxy)-2-oxoethyl]sulfonyl}amino)-1*H*-indole-6-carboxylate (D14) (13.4 g, 41.1 mmol) in dimethylformamide (145 ml) was treated with

potassium carbonate (19.8 g) and iodomethane (2.6 ml) and stirred overnight at room temperature. The mixture was evaporated and the residue diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate then the ethyl acetate layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by biotage (eluting with ethyl acetate:hexane) and the resulting solid was triturated with ether to give the title compound (D15) as an orange solid (4.93 g). $[M-H]^-$ = 339.2, RT = 2.38 min

Description 16

Dimethyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D16)

Phosphorus oxychloride (1.4 ml) was added dropwise to dimethylformamide (4.5 ml) at 0°C and the mixture was stirred for a further 15 minutes. The mixture was then treated with a solution of methyl 4-(methyl{[2-(methyloxy)-2-oxoethyl]sulfonyl}amino)-1*H*-indole-6-carboxylate (D15) (4.93 g, 14.5 mmol) in dimethylformamide (18 ml) and heated at 50°C for 1hr. A further amount of phosphorus oxychloride (0.7 ml) was added to the mixture and heating continued overnight at 60°C. The mixture was cooled and any excess phosphorus oxychloride and dimethylformamide was removed by evaporation. The residue was diluted carefully with dichloromethane (500 ml) and water (200 ml) and 2N aqueous sodium hydroxide was added until the pH of the aqueous layer was 7. Any solid that precipitated was collected by filtration and set aside. The dichloromethane layer was separated and then washed with water and dried over anhydrous sodium sulphate. Filtration and evaporation of the dichloromethane layer gave a yellow solid which was combined with the solid set aside previously. The solid was washed with dichloromethane and ether to give the title compound (D16) as a yellow solid (2.85g). $[M+H]^+$ = 351.1, RT = 2.27 min

Description 17

Dimethyl 6-ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D17)

A solution of dimethyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D16) (2.67 g, 7.63 mmol) in dimethylformamide (11 ml) was treated with sodium hydride (0.305 g, 60% suspension in oil) and stirred at room temperature for 10 minutes. The mixture was then treated with ethyl iodide (1.22 ml) and stirred overnight at room temperature. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and then with brine. The solid that precipitated at this stage was collected by filtration and washed with ether and water and then set aside. The remaining organic fraction was dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by trituration with ether and the resulting solid was combined with the solid collected earlier to give the title compound (D17) as a yellow solid (2.57 g). $[M+H]^+$ = 379.1, RT = 2.61 min

Description 18

Dimethyl 1-methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D18)

In a manner analogous to that described for the preparation of compound (D17), but using 2-iodopropane in the place of iodoethane, dimethyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D16) was reacted to give the title compound (D18) as a yellow solid. $[M+H]^+$ = 391.2, RT = 2.86 min

Description 19

Dimethyl 1-methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D19)

In a manner analogous to that described for the preparation of compound (D17), but using 1-bromopropane in the place of iodoethane, dimethyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D16) was reacted to give the title compound (D19) as a yellow solid. $[M+H]^+$ = 393.2, RT = 2.87 min

Description 20

Dimethyl 6-butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D20)

In a manner analogous to that described for the preparation of compound (D17), but using 1-iodobutane in the place of iodoethane, dimethyl 1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D16) was reacted to give the title compound (D20) as a yellow solid. $[M+Na]^+$ = 429.18, RT = 3.04 min

Description 21

6-Ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D21)

Dimethyl 6-ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D17) (2.57 g, 6.79 mmol) was dissolved in methanol (50 ml) and treated with 2N aqueous sodium hydroxide (50 ml) and then heated at reflux for 2 hours. The mixture was cooled and evaporated *in vacuo* and the residue was then taken up in ethyl acetate and acidified with 2M aqueous hydrogen chloride. The precipitate was collected by filtration and washed thoroughly with water and then with ether. Drying *in vacuo* gave the title compound (D21) as a yellow solid (2.02 g). $[M-H]^-$ = 349.2, RT = 1.82 min

Description 22

1-Methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D22)

In a manner analogous to that described for the preparation of compound (D21), dimethyl 1-methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-

dicarboxylate 2,2-dioxide (D18) was reacted to give the title compound (D22) as a gum. $[M-H]^-$ = 363.2, RT = 2.20 min

Description 23

1-Methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D23)

In a manner analogous to that described for the preparation of compound (D21), dimethyl 1-methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D19) was reacted to give the title compound (D23) as a yellow solid. $[M-H]^-$ = 363.2, RT = 2.23 min

Description 24

6-Butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D24)

In a manner analogous to that described for the preparation of compound (D21), dimethyl 6-butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylate 2,2-dioxide (D20) was reacted to give the title compound (D24) as a fawn solid. $[M-H]^-$ = 377.2, RT = 2.39 min

Preparation of Esters

Ester 1

Methyl 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C1)

A solution of methyl 1-ethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D11)(0.250 g, 0.82 mmol) in dimethylformamide (15 ml) was treated with a 60% suspension of sodium hydride in oil (0.034 g, 0.85 mmol) under an atmosphere of nitrogen. The mixture was stirred for 10 min and then iodoethane (0.156 g, 1.0 mmol) was added and stirring continued for a further 30 min. A further quantity of first sodium hydride (0.034 g, 0.85 mmol) and then iodoethane (0.156 g, 1.0 mmol) were added and the mixture was left to stand overnight. The solvent was evaporated *in vacuo* and the crude title compound (C1) thus obtained was used in the next step without further purification. $[M+H]^+$ = 335.2, RT = 2.83 min

Ester 2

Methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2)

A solution of methyl 1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (D13)(0.200 g, 0.68 mmol) in dimethylformamide (15 ml) was treated with a 60% suspension of sodium hydride in oil (0.034 g, 0.85 mmol) under a nitrogen atmosphere and stirred at room temperature for 10 min. The mixture was treated with iodoethane (0.156 g, 1.0 mmol) and stirring was continued for 30 min. The solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate and

washed sequentially with 2M aqueous hydrogen chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield crude title compound (C2)(0.250 g, 0.78 mmol). This was used without further purification in subsequent reactions. $[M+H]^+$ = 323.1, RT = 2.70 min

Preparation of Acids

Acid 1

6-Ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A1)

To a solution of methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2)(0.250 g, 0.78 mmol) in methanol (20 ml) was added 2N aqueous sodium hydroxide solution (10 ml, 20 mmol). The resulting mixture was heated at 50°C until the solution cleared and then the solvent was evaporated *in vacuo*. The residue was extracted with diethyl ether and then the aqueous layer was acidified using 2M aqueous hydrogen chloride and extracted twice with ethyl acetate. The ethyl acetate extracts were dried over $MgSO_4$, concentrated *in vacuo,* and then triturated with diethyl ether to give the title compound (A1)(0.150 g, 0.49 mmol) as a white solid, which was used in the next step without further purification. $[M+H]^+$ = 309.1, RT = 2.33 min

Acid 1 (Alternative Procedure)

6-Ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A1)

The title compound (A1) may be prepared in an analogous manner to that described for the synthesis of Acid 7 (A7) from 6-ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A3).

Acid 2

1,6-Diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2)

1,6-Diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2) was obtained in an analogous manner to that described for the synthesis of (A1) but using methyl 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C1) in the place of methyl 6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylate 2,2-dioxide (C2). $[M+H]^+$ = 321.2, RT = 2.45 min

Acid 3

6-Ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A3)

6-Ethyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D21) (2.16 g, 6.17mmol) was dissolved in 2N hydrogen chloride in dioxane (120 ml) and heated at reflux for 1 hour. The mixture was then cooled and evaporated *in vacuo* to give a solid. The solid was washed sequentially with water, ether, ethyl acetate, and then with ether again to give the title compound (A3) as a pale yellow solid (1.75 g). $[M+H]^+$ = 307.1, RT = 2.18 min

Acid 4

1-Methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A4)

In an analogous manner to that described for the synthesis of (A3), 1-methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D22) was reacted to give the title compound (A4) as a pale yellow solid. $[M+H]^+$ = 321.2, RT = 2.49 min

Acid 5

1-Methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A5)

In an analogous manner to that described for the synthesis of Acid 3 (A3), 1-methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D23) was reacted to give the title compound (A5) as a cream solid. $[M+H]^+$ = 321.2, RT = 2.55 min

Acid 6

6-Butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A6)

In an analogous manner to that described for the synthesis of Acid 3 (A3), 6-butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-3,8-dicarboxylic acid 2,2-dioxide (D24) was reacted to give the title compound (A6) as a fawn solid . $[M+H]^+$ = 355.09, RT = 2.65 min

Acid 7

1-Methyl-6-(1-methylethyl)-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A7)

A solution of 1-methyl-6-(1-methylethyl)-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A4) (0.22 g, 0.69 mmol) in ethanol:water (9:1, 20 ml) was treated with ammonium formate (0.44 g) and 10% palladium on carbon (0.1 g) and heated at 90°C for 3 hours. On cooling the mixture was filtered and evaporated to dryness *in vacuo.* The residue was dissolved in ethyl acetate and washed sequentially with saturated sodium hydrogen carbonate and water. The organic layer was dried over magnesium sulphate, then filtered and evaporated *in vacuo.* The residue was triturated with ether and the resulting solid was washed with water and then more ether before

drying to give the title compound (A7) as a white solid (0.12 g). $[M+H]^+$ = 323.2, RT = 2.57 min

Acid 8

1-Methyl-6-propyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A8)

In an analogous manner to that described for the synthesis of Acid 7 (A7), 1-methyl-6-propyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A5) was reacted to give the title compound (A8) as a white solid . $[M+H]^+$ = 323.2, RT = 2.56 min

Acid 9

6-Butyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A9)

In an analogous manner to that described for the synthesis of Acid (A7), 6-butyl-1-methyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A6) was reacted to give the title compound (A9) as a pale yellow solid (0.24 g). $[M+H]^+$ = 337.1, RT = 2.75 min

Acid 10

1,6-Diethyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A10)

In an analogous manner to that described for the synthesis of Acid (A7), 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2) was reacted to give the title compound (A10) as a white solid. $[M+H]^+$ = 323.2, RT = 2.50 min

Preparation of Amines

Amine 1 (B1)

(2R,3S)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol di-tosylate

Step A: ((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (10 g, 38 mmol) [Chirex 1819W94 Lot#9924382] was dissolved in ethanol (100 ml) and 3-methoxy-benzylamine (14.6 ml, 114 mmol) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in ethyl acetate and washed three times with water, dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel (dichloromethane/methanol: 98/2 to 95/5) gave [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (10.0 g, 66%) as a white solid.

Step B: To a solution of [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (product of B1, Step A) (10 g, 25 mmol) in acetonitrile (100 ml) was added *p*-toluenesulfonic acid monohydrate (14 g, 75 mmol) and

the resulting mixture was stirred for 16 h. The white precipitate formed was filtered and washed with diethyl ether then dried under vacuum to give the title compound (B1) (15.6 g) as a white solid which was used in the next step without further purification.

Amine 2

(2*R*,3*S*)-3-Amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2)

Step A: ((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (1.1 g, 4.1 mmol) [Chirex 1819W94 Lot#9924382] was dissolved in ethanol (100 ml) and tetrahydro-2*H*-pyran-4-ylamine (0.83 g, 8.22 mmol) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 4 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in ethyl acetate and washed three times with water, dried over magnesium sulfate and concentrated *in vacuo*. 1,1-Dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate was thus obtained as a white solid (0.95 g, 2.6 mmol). $[M+H]^+$ = 365.4, RT = 2.16 min

Step B: (2*R*,3*S*)-3-Amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2) was obtained in an analogous manner to that described for the synthesis of (B1) but using 1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate (product of B2, Step A) in the place of [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (product of B1, Step A).

Amines B3-82

Amines B3-82 were obtained in an analogous manner to that described for Amines 1 and 2 using ((S)-(S)-1-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (1.1 g, 4.1 mmol) [Chirex 1819W94 Lot#9924382] and the appropriate amine or an appropriate salt thereof (either obtained from commercial sources or prepared as described in WO 2004/094430). When the salt of the starting amine was used in place of the free base a molar equivalent of an appropriate base (such as triethylamine) was also added to the reaction mixture. The dihydrochloride salt of the amine was prepared in some cases in place of the ditosylate salt. These could be prepared in a manner analogous to that described for Amines (B1) and (B2) but using a solution of 4M HCl in dioxane in the place of *p*-toluenesulfonic acid monohydrate (as described in WO 2004/094430):

Amine No.	Name	Starting Amine (free base)
B3	(2*R*,3*S*)-3-Amino-4-phenyl-1-({[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]methyl}amino)-2-butanol ditosylate	{[1-(2,2,2-Trifluoroethyl)-1*H*-pyrazol-4-yl]methyl}amine
B4	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(phenylmethyl)amino]-2-butanol ditosylate	Benzylamine

B5	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(4-pyridinylmethyl)amino]-2-butanol ditosylate	(4-Pyridinylmethyl)amine
B6	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(3-pyridinylmethyl)amino]-2-butanol ditosylate	(3-Pyridinylmethyl)amine
B7	(2*R*,3*S*)-3-Amino-1-[(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)amino]-4-phenyl-2-butanol ditosylate	(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)amine
B8	(2*R*,3*S*)-3-Amino-1-{[(3-ethyl-5-isoxazolyl)methyl]amino}-4-phenyl-2-butanol dihydrochloride	[(3-Ethyl-5-isoxazolyl)methyl]amine
B9	(2*R*,3*S*)-3-Amino-1-(cyclobutylamino)-4-phenyl-2-butanol ditosylate	Cyclobutylamine
B10	(2*R*,3*S*)-3-Amino-1-[(4,4-difluorocyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(4,4-Difluorocyclohexyl)amine
B11	(2*R*,3*S*)-3-Amino-1-[(2-fluoroethyl)amino]-4-phenyl-2-butanol ditosylate	(2-Fluoroethyl)amine
B12	(2*R*,3*S*)-3-Amino-1-[(2,2,3,3,3-pentafluoropropyl)amino]-4-phenyl-2-butanol ditosylate	(2,2,3,3,3-Pentafluoropropyl)amine
B13	(2*R*,3*S*)-3-Amino-1-{[(5-ethyl-3-thienyl)methyl]amino}-4-phenyl-2-butanol ditosylate	[(5-Ethyl-3-thienyl)methyl]amine
B14	(2*R*,3*S*)-3-Amino-1-{[2-(methyloxy)ethyl]amino}-4-phenyl-2-butanol ditosylate	[2-(Methyloxy)ethyl]amine
B15	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(2,2,2-trifluoroethyl)amino]-2-butanol ditosylate	(2,2,2-Trifluoroethyl)amine
B16	(2*R*,3*S*)-3-Amino-1-(ethylamino)-4-phenyl-2-butanol ditosylate	Ethylamine
B17	(2*R*,3*S*)-3-Amino-1-[(cyclopropylmethyl)amino]-4-phenyl-2-butanol ditosylate	(Cyclopropylmethyl)amine
B18	(2*R*,3*S*)-3-Amino-1-(cyclohexylamino)-4-phenyl-2-butanol ditosylate	Cyclohexylamine
B19	(2*R*,3*S*)-3-amino-1-(3-cyclopenten-1-ylamino)-4-phenyl-2-butanol ditosylate	3-Cyclopenten-1-ylamine
B20	(2*R*,3*S*)-3-Amino-1-{[2-(ethylthio)ethyl]amino}-4-phenyl-2-butanol ditosylate	2-(Ethylthio)ethanamine
B21	(2*R*,3*S*)-3-Amino-1-[(4-	(4-Methylcyclohexyl)amine

	methylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	
B22	(2*R*,3*S*)-3-Amino-4-phenyl-1-({[3-(trifluoromethyl)phenyl]methyl}amino)-2-butanol ditosylate	{[3-(Trifluoromethyl)phenyl]methyl} amine
B23	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(1-propylbutyl)amino]-2-butanol ditosylate	(1-Propylbutyl)amine
B24	(2*R*,3*S*)-3-Amino-1-[(4,4-dimethylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(4,4-Dimethylcyclohexyl)amine
B25	(2*R*,3*S*)-3-Amino-4-phenyl-1-(2-propyn-1-ylamino)-2-butanol ditosylate	2-Propyn-1-ylamine
B26	(2*R*,3*S*)-3-Amino-4-phenyl-1-(2-propen-1-ylamino)-2-butanol ditosylate	2-Propen-1-ylamine
B27	(2*R*,3*S*)-3-Amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol ditosylate	(3,3-Dimethylbutyl)amine
B28	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(3,3,5,5-tetramethylcyclohexyl)amino]-2-butanol ditosylate	(3,3,5,5-Tetramethylcyclohexyl)amine
B29	(2*R*,3*S*)-3-Amino-1-[(1,5-dimethylhexyl)amino]-4-phenyl-2-butanol dihydrochloride	(1,5-Dimethylhexyl)amine
B30	(2*R*,3*S*)-3-Amino-4-phenyl-1-(propylamino)-2-butanol dihydrochloride	Propylamine
B31	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(3,3,3-trifluoropropyl)amino]-2-butanol ditosylate	(3,3,3-Trifluoropropyl)amine
B32	(2*R*,3*S*)-3-Amino-1-[(2,2-difluoroethyl)amino]-4-phenyl-2-butanol ditosylate	(2,2-Difluoroethyl)amine
B33	(2*R*,3*S*)-3-Amino-1-[(2-ethylbutyl)amino]-4-phenyl-2-butanol ditosylate	(2-Ethylbutyl)amine
B34	(2*R*,3*S*)-3-Amino-1-[(3-methylbutyl)amino]-4-phenyl-2-butanol ditosylate	(3-Methylbutyl)amine
B35	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(2,2,6,6-tetramethylcyclohexyl)amino]-2-butanol ditosylate	(2,2,6,6-Tetramethylcyclohexyl)amine
B36	(2*R*,3*S*)-3-Amino-1-[(2,2-dimethylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(2,2-Dimethylcyclohexyl)amine

B37	(2*R*,3*S*)-3-Amino-1-{[2-(methylthio)ethyl]amino}-4-phenyl-2-butanol ditosylate	[2-(Methylthio)ethyl]amine
B38	(2*R*,3*S*)-3-Amino-1-[(2-cyclohexylethyl)amino]-4-phenyl-2-butanol ditosylate	(2-Cyclohexylethyl)amine
B39	(2*R*,3*S*)-3-Amino-1-[(2-methyl-2-propen-1-yl)amino]-4-phenyl-2-butanol ditosylate	(2-Methyl-2-propen-1-yl)amine
B40	(2*R*,3*S*)-3-Amino-1-(3-buten-1-ylamino)-4-phenyl-2-butanol ditosylate	3-Buten-1-ylamine
B41	(2*R*,3*S*)-3-Amino-1-(cycloheptylamino)-4-phenyl-2-butanol ditosylate	Cycloheptylamine
B42	(2*R*,3*S*)-3-Amino-4-phenyl-1-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-2-butanol ditosylate	(1*R*,3*S*,5*R*,7*S*)-Tricyclo[3.3.1.1^{3,7}]dec-2-ylamine
B43	(2*R*,3*S*)-3-Amino-1-[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-ylamino]-4-phenyl-2-butanol ditosylate	(1*S*,4*R*)-Bicyclo[2.2.1]hept-2-ylamine
B44	(2*R*,3*S*)-3-Amino-4-phenyl-1-{[2-(propyloxy)ethyl]amino}-2-butanol ditosylate	[2-(Propyloxy)ethyl]amine
B45	(2*R*,3*S*)-3-Amino-1-[(1-ethynylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(1-Ethynylcyclohexyl)amine
B46	(2*R*,3*S*)-3-Amino-1-[(4-methylphenyl)amino]-4-phenyl-2-butanol ditosylate	4-Methylaniline
B47	(2*R*,3*S*)-3-Amino-1-[(1-methylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(1-Methylcyclohexyl)amine
B48	(2*R*,3*S*)-3-Amino-1-[(1-ethylcyclohexyl)amino]-4-phenyl-2-butanol ditosylate	(1-Ethylcyclohexyl)amine
B49	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(1-propylcyclohexyl)amino]-2-butanol ditosylate	(1-Propylcyclohexyl)amine
B50	(2*R*,3*S*)-3-Amino-1-({2-[(1,1-dimethylethyl)thio]ethyl}amino)-4-phenyl-2-butanol ditosylate	{2-[(1,1-Dimethylethyl)thio]ethyl}amine
B51	(2*R*,3*S*)-3-Amino-4-phenyl-1-({2-[(2,2,2-trifluoroethyl)oxy]ethyl}amino)-2-butanol ditosylate	{2-[(2,2,2-Trifluoroethyl)oxy]ethyl}amine

B52	(2*R*,3*S*)-3-Amino-4-phenyl-1-(phenylamino)-2-butanol ditosylate	Aniline
B53	(2*R*,3*S*)-3-Amino-1-[(3-methylphenyl)amino]-4-phenyl-2-butanol ditosylate	3-Methylaniline
B54	(2*R*,3*S*)-3-Amino-1-[(2-methylphenyl)amino]-4-phenyl-2-butanol ditosylate	2-Methylaniline
B55	(2*R*,3*S*)-3-Amino-1-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-phenyl-2-butanol ditosylate	[(1-Ethyl-1*H*-pyrazol-4-yl)methyl]amine
B56	(2*R*,3*S*)-3-Amino-1-[(3-methyl-2-buten-1-yl)amino]-4-phenyl-2-butanol ditosylate	(3-Methyl-2-buten-1-yl)amine
B57	(2*R*,3*S*)-3-Amino-1-[(2-chlorophenyl)amino]-4-phenyl-2-butanol ditosylate	2-Chloroaniline
B58	(2*R*,3*S*)-3-Amino-1-{[2-(methyloxy)phenyl]amino}-4-phenyl-2-butanol ditosylate	2-Methoxyaniline
B59	(2*R*,3*S*)-3-Amino-1-{[4-(methyloxy)phenyl]amino}-4-phenyl-2-butanol ditosylate	4-Methoxyaniline
B60	(2*R*,3*S*)-3-Amino-1-[(3-chlorophenyl)amino]-4-phenyl-2-butanol ditosylate	3-Chloroaniline
B61	(2*R*,3*S*)-3-Amino-1-{[3-(methyloxy)phenyl]amino}-4-phenyl-2-butanol ditosylate	3-Methoxyaniline
B62	(2*R*,3*S*)-3-Amino-1-[(4-chlorophenyl)amino]-4-phenyl-2-butanol ditosylate	4-Chloroaniline
B63	(2*R*,3*S*)-3-Amino-1-(cyclopropylamino)-4-phenyl-2-butanol ditosylate	Cyclopropylamine
B64	(2*R*,3*S*)-3-Amino-1-[(2,4-dimethylphenyl)amino]-4-phenyl-2-butanol ditosylate	2,4-Dimethylaniline
B65	(2*R*,3*S*)-3-Amino-1-{[4-(dimethylamino)phenyl]amino}-4-phenyl-2-butanol ditosylate	*N*,*N*-Dimethyl-1,4-benzenediamine
B66	(2*R*,3*S*)-3-Amino-1-(2-butyn-1-ylamino)-4-phenyl-2-butanol ditosylate	2-Butyn-1-ylamine

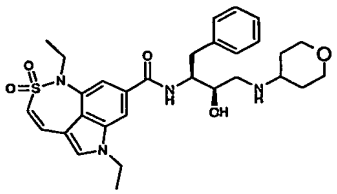
B67	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(1,1,5-trimethylhexyl)amino]-2-butanol ditosylate	(1,1,5-Trimethylhexyl)amine
B68	(2*R*,3*S*)-3-Amino-1-(butylamino)-4-phenyl-2-butanol ditosylate	Butylamine
B69	(2*R*,3*S*)-3-Amino-1-(cyclooctylamino)-4-phenyl-2-butanol ditosylate	Cyclooctylamine
B70	(2*R*,3*S*)-3-Amino-1-{[2,3-bis(methyloxy)phenyl]amino}-4-phenyl-2-butanol ditosylate	[2,3-Bis(methyloxy)phenyl]amine
B71	(2*R*,3*S*)-3-Amino-4-phenyl-1-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]-2-butanol ditosylate	({3-[(Trifluoromethyl)oxy]phenyl}methyl)amine
B72	(2*R*,3*S*)-3-Amino-1-{[(6-methyl-2-pyridinyl)methyl]amino}-4-phenyl-2-butanol ditosylate	[(6-Methyl-2-pyridinyl)methyl]amine
B73	N^2-[(2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutyl]-N^1-cyclohexyl-L-alaninamide dihydrochloride	N^1-Cyclohexyl-L-alaninamide
B74	(2*R*,3*S*)-3-Amino-1-{[(1*R*)-1-methylpropyl]amino}-4-phenyl-2-butanol ditosylate	[(1*R*)-1-Methylpropyl]amine
B75	(2*R*,3*S*)-3-Amino-1-{[(1*S*)-1-methylpropyl]amino}-4-phenyl-2-butanol ditosylate	[(1*S*)-1-Methylpropyl]amine
B76	(2*R*,3*S*)-3-Amino-4-phenyl-1-[(2-pyridinylmethyl)amino]-2-butanol ditosylate	(2-Pyridinylmethyl)amine
B77	(2*R*,3*S*)-3-Amino-1-{[2-methyl-4-(methyloxy)phenyl]amino}-4-phenyl-2-butanol ditosylate	2-Methyl-4-(methyloxy)aniline
B78	(2*R*,3*S*)-3-Amino-1-[(1-ethylcyclopropyl)amino]-4-phenyl-2-butanol ditosylate	(1-Ethylcyclopropyl)amine
B79	(2*R*,3*S*)-3-Amino-1-(2-pentyn-1-ylamino)-4-phenyl-2-butanol ditosylate	2-Pentyn-1-ylamine
B80	(2*R*,3*S*)-3-Amino-1-[(3-fluoropropyl)amino]-4-phenyl-2-butanol ditosylate	(3-Fluoropropyl)amine
B81	(2*R*,3*S*)-3-Amino-1-[(1-methylcyclopropyl)amino]-4-phenyl-2-butanol ditosylate	(1-Methylcyclopropyl)amine

B82	(2*R*,3*S*)-3-Amino-1-[(1,1-dimethyl-2-propyn-1-yl)amino]-4-phenyl-2-butanol ditosylate	(1,1-Dimethyl-2-propyn-1-yl)amine

Examples

Example 1

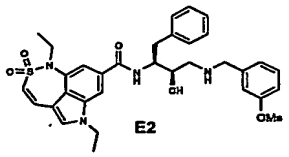
1,6-Diethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E1)

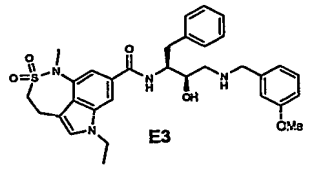
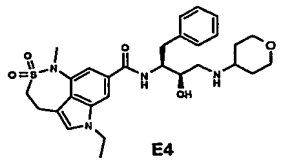
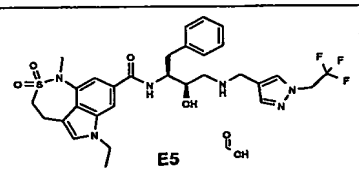
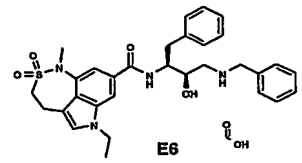
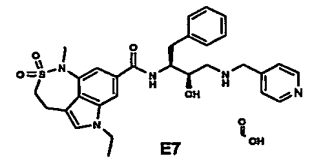


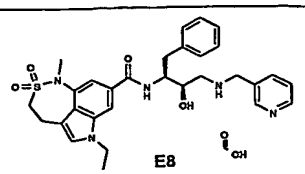
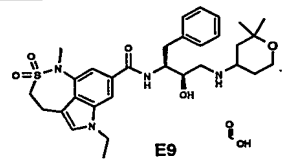
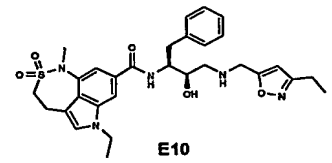
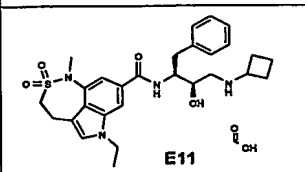
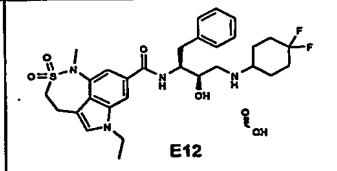
To a solution of 1,6-diethyl-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxylic acid 2,2-dioxide (A2) (0.038 g, 0.12 mmol) in dimethylformamide (3 ml) was added (2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol di-tosylate (B2)(0.730 g, 0.12 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.030 g, 0.15 mmol), 1-hydroxybenzotriazole hydrate (0.025 g, 0.15 mmol), and triethylamine (0.100 ml, 0.72 mmol). The mixture was stirred overnight at room temperature and then the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated to give the crude product. Purification by biotage (eluting with 2-5% methanol in dichloromethane) and freeze-drying gave the title compound (E1) (0.030 g, 0.05 mmol) as a white solid.
$[M+H]^+$ = 567.6, RT = 2.3 min.

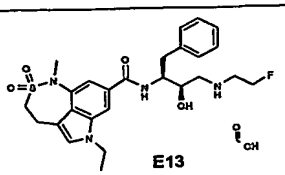
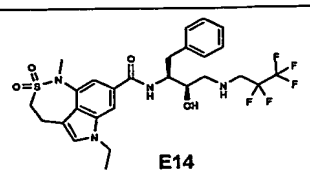
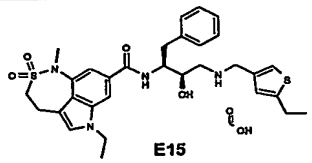
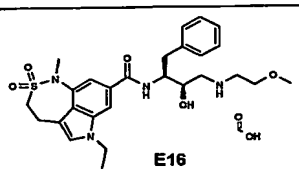
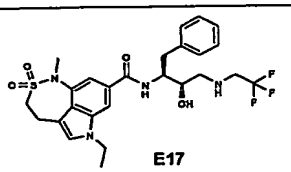
Examples 2-89 (E2-E89)

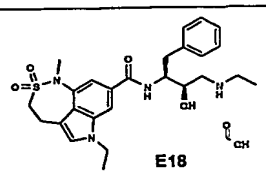
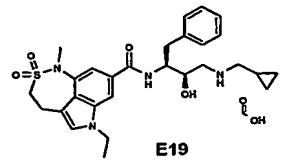
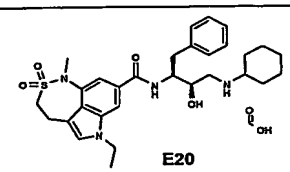
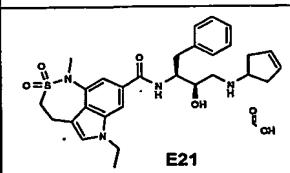
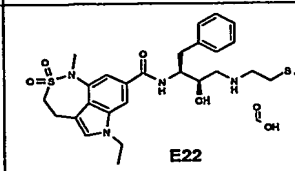
Examples 2-89 were obtained in an analogous procedure (in examples where the formate salt is indicated the compounds were purified by mass-directed automated preparative HPLC using acetonitrile/water/formic acid as the eluant rather than by biotage as indicated above) to that described for Example 1 using the appropriate acid and the appropriate amine indicated in the table below:

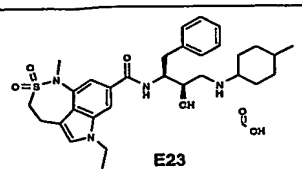
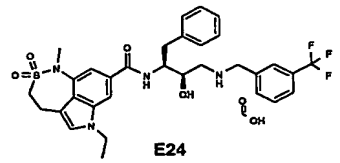
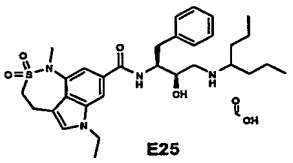
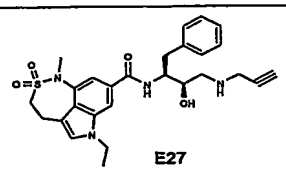
Example	Structure	Acid	Amine	$[M+H]^+$	RT (min)
1,6-Diethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-	 E2	A2	B1	603.5	2.5

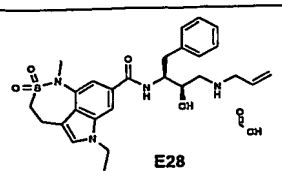
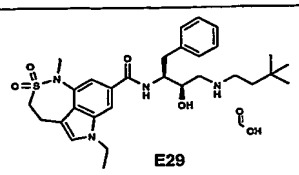
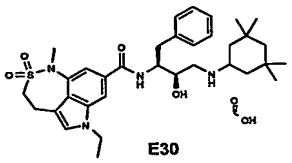
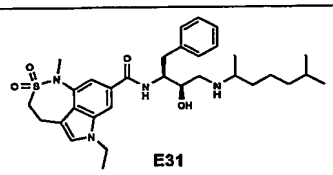
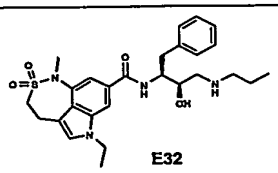
cd]indole-8-carboxamide 2,2-dioxide (E2)					
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2] thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E3)	 E3	A1	B1	591.5	2.5
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2] thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E4)	 E4	A1	B2	555.5	2.2
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]methyl}amino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E5)	 E5	A1	B3	633.4	2.5
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(phenylmethyl)amino]propyl} -1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E6)	 E6	A1	B4	561.5	2.5
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(4-pyridinylmethyl)amino]propyl} -1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E7)	 E7	A1	B5	562.4	2.3

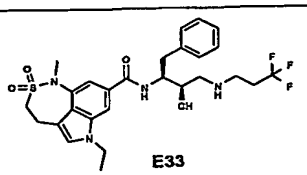
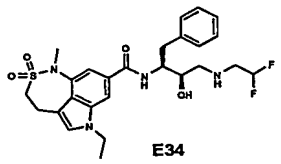
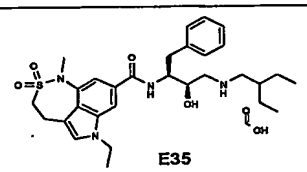
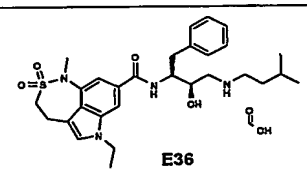
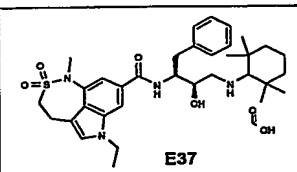
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(3-pyridinylmethyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E8)	 E8	A1	B6	562.4	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-[(2,2-Dimethyltetrahydro-2*H*-pyran-4-yl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E9)	 E9	A1	B7	583.4	2.4
6-Ethyl-*N*-[(1*S*,2*R*)-3-{[(3-ethyl-5-isoxazolyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E10)	 E10	A1	B8	580.1	2.4
Formic acid - *N*-[(1*S*,2*R*)-3-(Cyclobutylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E11)	 E11	A1	B9	525.4	2.4
Formic acid - *N*-[(1*S*,2*R*)-3-[(4,4-Difluorocyclohexyl) amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E12)	 E12	A1	B10	588.5	2.5

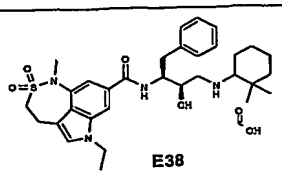
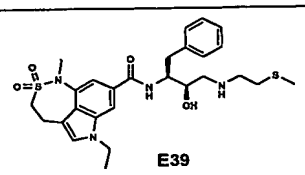
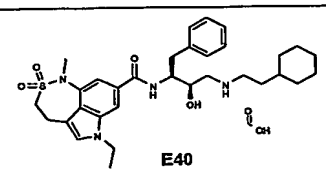
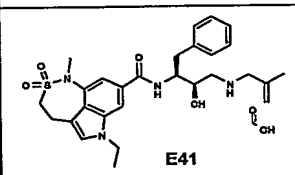
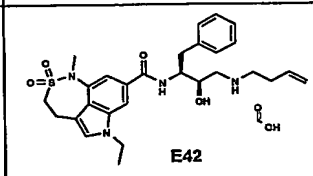
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(2-fluoroethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E13)	 E13	A1	B11	517.5	2.3
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(2,2,3,3,3-pentafluoropropyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E14)	 E14	A1	B12	604.5	3.2
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-{[(5-ethyl-3-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E15)	 E15	A1	B13	595.5	2.7
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[2-(methyloxy)ethyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E16)	 E16	A1	B14	529.5	2.2
6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(2,2,2-trifluoroethyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E17)	 E17	A1	B15	553.4	2.3

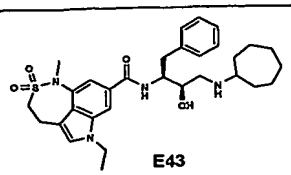
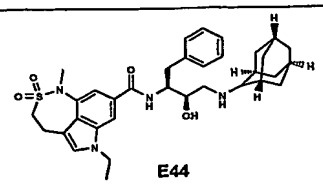
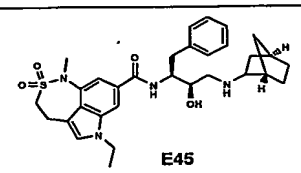
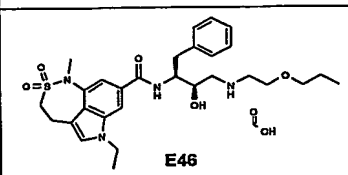
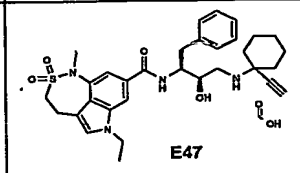
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-(ethylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E18)	 E18	A1	B16	499.5	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-[(Cyclopropylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E19)	 E19	A1	B17	525.5	2.4
Formic acid - *N*-[(1*S*,2*R*)-3-(Cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E20)	 E20	A1	B18	553.5	2.5
Formic acid - *N*-[(1*S*,2*R*)-3-(3-Cyclopenten-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E21)	 E21	A1	B19	537.5	2.4
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-{[2-(ethylthio)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E22)	 E22	A1	B20	559.4	2.5

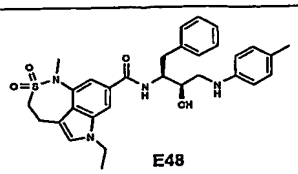
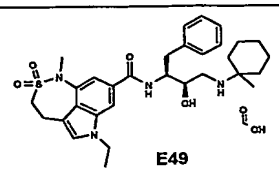
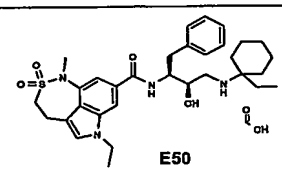
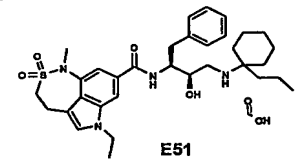
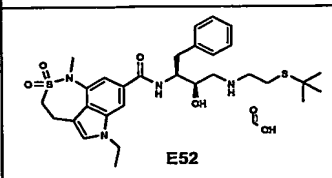
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(4-methylcyclohexyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E23)	 E23	A1	B21	567.5	2.7
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E24)	 E24	A1	B22	629.4	2.8
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylbutyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E25)	 E25	A1	B23	569.5	2.7
Formic acid - *N*-[(1*S*,2*R*)-3-[(4,4-Dimethylcyclohexyl) amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E26)	 E26	A1	B24	581.5	2.7
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(2-propyn-1-ylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E27)	 E27	A1	B25	509.5	2.2

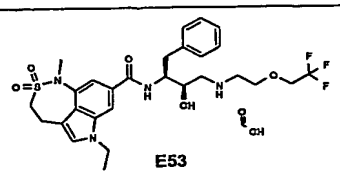
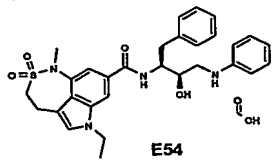
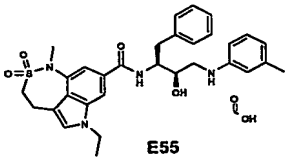
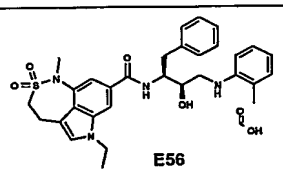
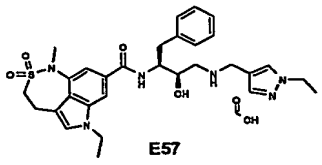
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(2-propen-1-ylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E28)	 E28	A1	B26	511.4	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-[(3,3-Dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl) propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E29)	 E29	A1	B27	555.5	2.6
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(3,3,5,5-tetramethylcyclohexyl)amino] propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E30)	 E30	A1	B28	609.3	2.9
N-[(1*S*,2*R*)-3-[(1,5-Dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E31)	 E31	A1	B29	583.5	2.8
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(propylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E32)	 E32	A1	B30	513.5	2.3

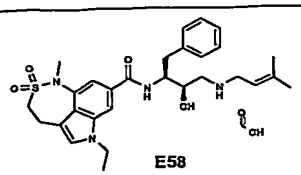
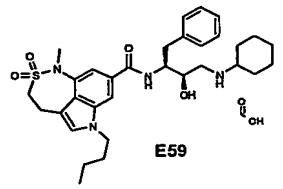
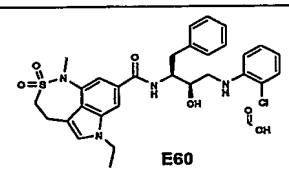
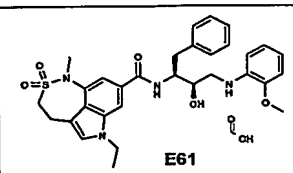
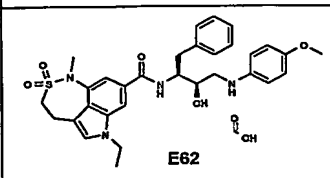
6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(3,3,3-trifluoropropyl)amino] propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E33)	 E33	A1	B31	567.5	2.4
N-[(1*S*,2*R*)-3-[(2,2-Difluoroethyl)amino]-2-hydroxy-1-(phenylmethyl) propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2] thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E34)	 E34	A1	B32	535.5	2.3
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(2-ethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E35)	 E35	A1	B33	555.5	2.2
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(3-methylbutyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E36)	 E36	A1	B34	541.5	2.1
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(2,2,6,6-tetramethylcyclohexyl)amino] propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E37)	 E37	A1	B35	609.5	2.7

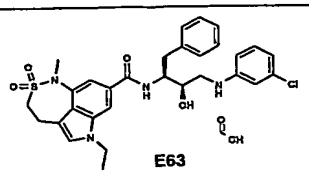
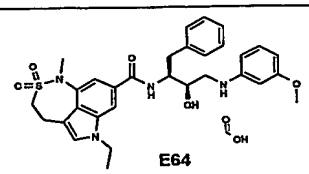
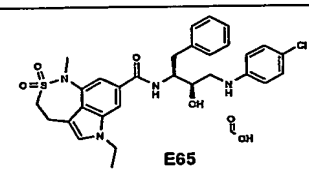
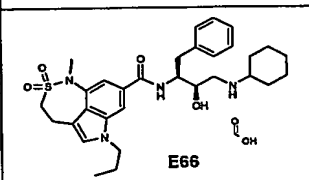
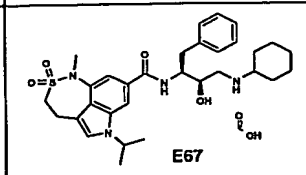
Formic acid - *N*-[(1*S*,2*R*)-3-[(2,2-Dimethylcyclohexyl) amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E38)	 E38	A1	B36	581.5	2.5
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[2-(methylthio)ethyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E39)	 E39	A1	B37	545.4	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-[(2-Cyclohexylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E40)	 E40	A1	B38	581.5	2.8
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(2-methyl-2-propen-1-yl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E41)	 E41	A1	B39	525.5	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-(3-Buten-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E42)	 E42	A1	B40	525.5	2.3

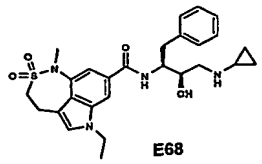
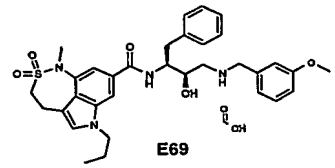
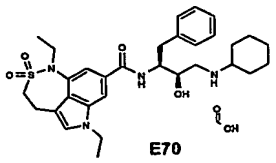
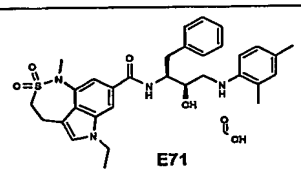
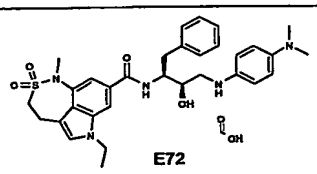
N-[(1*S*,2*R*)-3-(Cycloheptylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E43)	 E43	A1	B41	567.5	2.0
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E44)	 E44	A1	B42	607.6	2.14
N-[(1*S*,2*R*)-3-[(1*S*,4*R*)-Bicyclo[2.2.1]hept-2-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E45)	 E45	A1	B43	567.6	2.04
Formic acid - 6-Ethyl-*N*-((1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-{[2-(propyloxy)ethyl]amino} propyl)-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E46)	 E46	A1	B44	557.3	1.8
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(1-ethynylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E47)	 E47	A1	B45	577.3	2.2

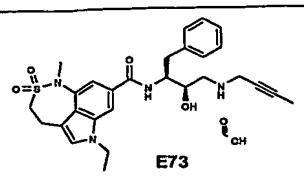
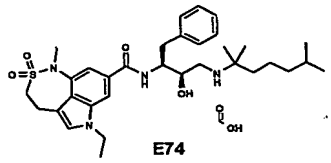
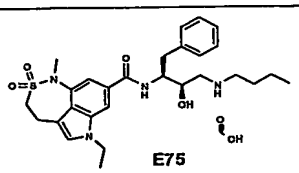
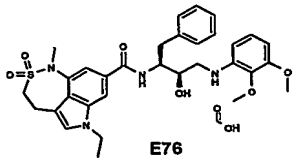
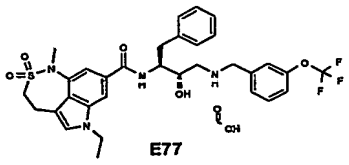
6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(4-methylphenyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E48)	 E48	A1	B46	559.3	2.8
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclohexyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E49)	 E49	A1	B47	565.5	1.9
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(1-ethylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E50)	 E50	A1	B48	581.4	2.3
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclohexyl)amino] propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E51)	 E51	A1	B49	593.6	2.1
Formic acid - *N*-[(1*S*,2*R*)-3-({2-[(1,1-Dimethylethyl)thio]ethyl} amino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E52)	 E52	A1	B50	587.4	2.2

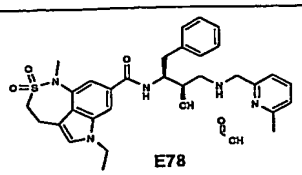
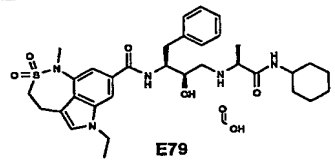
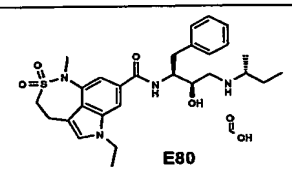
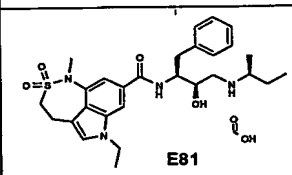
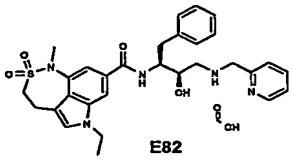
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({2-[(2,2,2-trifluoroethyl)oxy]ethyl}amino) propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E53)	 E53	A1	B51	597.4	2.1
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-(phenylamino)-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E54)	 E54	A1	B52	547.4	2.9
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(3-methylphenyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E55)	 E55	A1	B53	561.4	2.9
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(2-methylphenyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E56)	 E56	A1	B54	561.4	3.0
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E57)	 E57	A1	B55	579.3	2.1

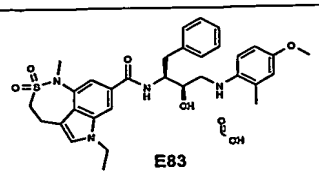
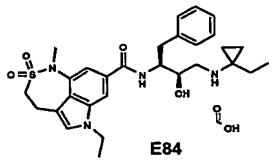
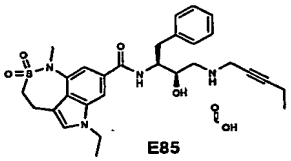
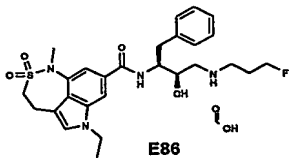
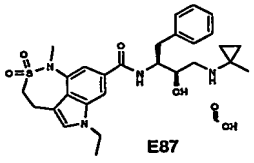
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(3-methyl-2-buten-1-yl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E58)	 E58	A1	B56	539.3	2.2
Formic acid - 6-Butyl-*N*-[(1*S*,2*R*)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E59)	 E59	A9	B18	581.3	2.4
Formic acid - *N*-[(1*S*,2*R*)-3-[(2-Chlorophenyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E60)	 E60	A1	B57	581.2	3.1
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[2-(methyloxy)phenyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E61)	 E61	A1	B58	577.3	2.9
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[4-(methyloxy)phenyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E62)	 E62	A1	B59	577.3	2.3

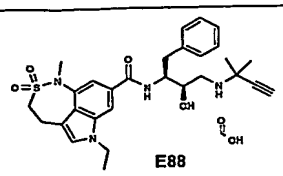
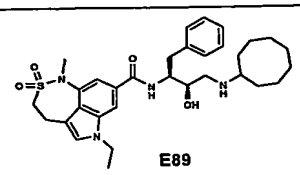
Formic acid - *N*-[(1*S*,2*R*)-3-[(3-Chlorophenyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E63)	 E63	A1	B60	581.2	3.0
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[3-(methyloxy)phenyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E64)	 E64	A1	B61	577.3	2.8
Formic acid - *N*-[(1*S*,2*R*)-3-[(4-Chlorophenyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E65)	 E65	A1	B62	581.2	3.0
Formic acid - *N*-[(1*S*,2*R*)-3-(Cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-6-propyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E66)	 E66	A8	B18	567.3	2.3
Formic acid - *N*-[(1*S*,2*R*)-3-(Cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-6-(1-methylethyl)-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E67)	 E67	A7	B18	567.3	2.2

N-[(1*S*,2*R*)-3-(Cyclopropylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E68)	 E68	A1	B63	511.3	2.0
Formic acid - *N*-[(1*S*,2*R*)-2-Hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-1-methyl-6-propyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E69)	 E69	A8	B1	605.4	2.2
Formic acid - *N*-[(1*S*,2*R*)-3-(Cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1,6-diethyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E70)	 E70	A10	B18	567.4	2.1
Formic acid - *N*-[(1*S*,2*R*)-3-[(2,4-Dimethylphenyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E71)	 E71	A1	B64	575.4	2.9
Formic acid - *N*-[(1*S*,2*R*)-3-{[4-(Dimethylamino)phenyl] amino}-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E72)	 E72	A1	B65	590.4	2.1

Formic acid - *N*-[(1*S*,2*R*)-3-(2-Butyn-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E73)	 E73	A1	B66	523.3	2.1
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E74)	 E74	A1	B67	597.5	2.4
Formic acid - *N*-[(1*S*,2*R*)-3-(Butylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E75)	 E75	A1	B68	527.4	2.1
Formic acid - *N*-[(1*S*,2*R*)-3-{[2,3-Bis(methyloxy)phenyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E76)	 E76	A1	B70	607.4	2.9
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E77)	 E77	A1	B71	645.4	2.3

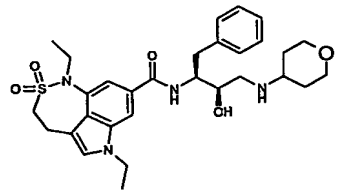
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[(6-methyl-2-pyridinyl)methyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E78)	 E78	A1	B72	576.4	2.2
Formic acid - *N*-[(1*S*,2*R*)-3-{[(1*S*)-2-(Cyclohexylamino)-1-methyl-2-oxoethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E79)	 E79	A1	B73	624.5	2.2
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[(1*R*)-1-methylpropyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E80)	 E80	A1	B74	527.4	2.1
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[(1*S*)-1-methylpropyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E81)	 E81	A1	B75	527.4	2.1
Formic acid - 6-Ethyl-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(2-pyridinylmethyl)amino]propyl}-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E82)	 E82	A1	B76	562.3	2.1

Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-{[2-methyl-4-(methyloxy)phenyl]amino}-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E83)	 E83	A1	B77	591.2	2.2
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(1-ethylcyclopropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E84)	 E84	A1	B78	539.3	2.1
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-(2-pentyn-1-ylamino)-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E85)	 E85	A1	B79	537.3	2.1
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-3-[(3-fluoropropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E86)	 E86	A1	B80	531.3	2.0
Formic acid - 6-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclopropyl)amino]-1-(phenylmethyl)propyl]-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide	 E87	A1	B81	525.4	2.1

2,2-dioxide (1:1) (E87)					
Formic acid - *N*-[(1*S*,2*R*)-3-[(1,1-Dimethyl-2-propyn-1-yl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (1:1) (E88)	 E88	A1	B82	537.6	1.9
N-[(1*S*,2*R*)-3-(Cyclooctylamino)-2-hydroxy-1-(phenylmethyl)propyl]-6-ethyl-1-methyl-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E89)	 E89	A1	B69	581.5	2.1

Example 90

1,6-Diethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,3,4,6-tetrahydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E90)



A solution of 1,6-diethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,6-dihydro[1,2]thiazepino[5,4,3-*cd*]indole-8-carboxamide 2,2-dioxide (E1) (0.010 g, 0.02 mmol) in methanol (5 ml) was treated with ammonium formate (0.020 g, 0.32 mmol) and 10% palladium on charcoal (0.015 g) and heated at reflux for 1h. The mixture was filtered and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (30 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated *in vacuo*. Freeze-drying gave the title compound (E90) (0.005 g, 0.01 mmol) as a white solid. $[M+H]^+$ = 569.6, RT = 2.3 min.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Asp-2 inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-

a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).
b) 10 μl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.
c) 10 μl enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

(II) Cathepsin D inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-
a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).
b) 10 μl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid).
c) 10 μl enzyme solution. This is prepared by diluting 1.6ml of a 200 unit/ml (in 10 mM HCl) enzyme solution into 398.4 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

The compounds of E1-E90 were tested in Assays (I) and (II) and exhibited inhibition within the following range: 2nM – 10μM (Asp2) and 30nM - >100μM (CatD).

Abbreviations

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMAP	dimethylaminophenol
DABCO	1,4-diazabicyclo [2.2.2] octane
DME	dimethyl ether
THF	tetrahydrofuran
HOBT	N-hydroxybenzotriazole
FAM	carboxyfluorescein
TAMRA	carboxytetramethylrhodamine
[ ]	single amino acid letter code relating to peptide sequence